Mid-cycle Meeting Summary
BLA 125596/0
February 26, 2016

Application type and number:	BLA 125596/0
Product name:	Immune Globulin Subcutaneous (Human), 20% Solution [Cuvitru]
Proposed Indication:	To treat primary immune deficiency disorders associated with defects in humoral immunity.
Applicant:	Baxalta US Inc.
Meeting date & time:	February 26, 2016, 3 pm – 4:30 pm, ET
Committee Chair:	Jennifer Reed, PhD
RPM:	LT Thomas J. Maruna, USPHS, MSc, MLS(ASCP), CPH

Attendees:

Meghna Alimchandani, MD (CBER/OBE)
Qiao Bobo, PhD (CBER/OCBQ/DMPQ)
Karen Campbell (CBER/OCBQ/DBSQC)
Howard Chazin, MD, MBA (CBER/OBRR/DHCR)
Jay Eltermann (CBER/OCBQ/DMPQ)
Mahmood Farshid, PhD (CBER/OBRR/DHRR)
Lisa Faulcon, MD (CBER/OBRR/DHCR/CRB)
Mitchell Frost, MD (CBER/OBRR/DHCR/CRB)
Patricia Holobaugh (CBER/OCBQ/BIMO)
Colonious King (CBER/OCBQ/BIMO)
Mark Levi, PhD (CBER/OCBQ/DBSQC)
Anthony Lorenzo, PhD (CBER/OCBQ/DMPQ)
Thomas J. Maruna, MSc, MLS(ASCP), CPH (CBER/OBRR/IO)
Mikhail Ovanesov, PhD (CBER/OBRR/DHRR)
Anne M. Pilaro, PhD (CBER/OBRR/DHCR)
Alpita Popat, PharmD (CBER/OCBQ/DCM/APLB)
Jennifer Reed, PhD (CBER/OBRR/DHRR/LPD)
Renee Rees, PhD (CBER/OBE/DB)
Olga Simakova, PhD (CBER/OBRR/DHRR/LPD)
Emily Storch, MD (CBER/OBRR/DHCR/CRB)
Evi Struble, PhD (CBER/OBRR/DHRR/LPD)
Iliana Valencia, MS (CBER/OBRR/IO)
Hsiaoling Wang, PhD (CBER/OCBQ/DBSQC)
Claire Wernly, MLT(ASCP) (CBER/OCBQ/DBSQC)
Boris Zaslavsky, PhD (CBER/OBE/DB)

1. Discussion Summary (Discipline Reviews):

Chemistry Manufacturing and Controls (CMC): Product, Facilities and In-Support Testing:
The Applicant's Immune Globulin Subcutaneous (Human), 20% Solution (IGSC, 20%) product is (b) (4). Process validation for the new manufacturing steps appears adequate. A small number of conformance and clinical batches were manufactured by the Applicant, in separate campaigns, using routine (b) (4) intermediate manufactured using the licensed process. There were small differences in the final manufacturing steps used in the clinical and conformance lot campaigns. Nevertheless, the conformance and clinical final product batches were highly similar to each other. Manufacturing deviations (sterile filter reduced flow rate) associated with the conformance lot campaign were addressed in a pre-BLA meeting. Investigations and CAPAs were deemed adequate at that time. Clinical and conformance lots met all release specifications. Extended analysis included (b) (4) assessment, which was inadequate and requires follow-up. As expected, IGSC 20% has a slightly worse stability profile than IGI, 10%. The stability data presented are supportive of the Applicant's proposed storage conditions and shelf life.

In this electronic BLA submission the Applicant introduces Cuvitru, an IGSC, 20% preparation highly similar to the Applicant's approved Gammagard Liquid IGI, 10% product. The IGSC, 20% product differs in the (b) (4) and formulation steps, and is intended for subcutaneous route of administration only. The manufacturing process from starting plasma (b) (4).

Manufacturing Overview: Drug Substance
Manufacturing of IGSC, 20% (b) (4).
For manufacturing IGSC, 20% the Applicant utilizes a modified Cohn-Oncley cold ethanol fractionation procedure to isolate an intermediate fraction called (b) (4) from (b) (4) human plasma. Fractionation of starting plasma and (b) (4) production occurs in the Applicant's currently licensed facilities in (b) (4). (b) (4) batches from the three facilities are shipped (b) (4) to the Applicant's facility in (b) (4) for further processing. Immune globulin is isolated from (b) (4) by cation and anion exchange chromatography. Pathogen inactivation and removal are effected by three dedicated steps: solvent/detergent treatment, nanofiltration, and low pH / elevated temperature hold during final formulation. (b) (4) glycine buffer at pH (b) (4) achieves the desired formulation criteria of pH 4.6-5.1 and a concentration of huIgG between (b) (4).

Validation of Upstream Manufacturing Steps in IGSC, 20% Process
Essentially all data presented to support upstream manufacturing steps in IGSC 20% were previously submitted to support the Applicant's IGI, 10% BLA. Importantly:

1) Critical process controls and study reports justifying limits including virus inactivation by S/D and nanofiltration parameters were submitted, reviewed, and approved as part of IGI, 10% licensure.
2) Characterization of impurities and analysis of purification steps which remove impurities were all submitted previously to the IGI, 10% BLA.
3) Data supporting comparability of (b) (4) batches prepared at (b) (4) facilities were submitted to the IGI, 10% BLA.
4) Validation studies of analytical methods was similarly submitted and approved previously.

The Applicant does note (b) (4)

Information Provided on Drug Product Manufacture: General

The drug product is a purified 20% IgG isotonic solution, containing approximately 200 mg protein per mL of which at least 98% is IgG, with a pH of 4.6 to 5.1 and glycine stabilizing agent at (b) (4). Composition of the biologic product is shown in Table 1, below.

Table 1. Target Composition of IGSC, 20%

Name of Component	Unit and/or Percentage Formula				Function	Reference to Standard
Protein (with at least 98% IgG)	1 g/vial	2 g/vial	4 g/vial	8 g/vial	Active ingredient	(b) (4)
	Other Ingredients					
Glycine	(b) (4)				Stabilizing agent	
Water for injection to a final volume of:	5 mL	10 mL	20 mL	40 mL	Drug carrier	

The Applicant notes that (b) (4) batches are generated from (b) (4) of plasma. At (b) (4), (b) (4) batches are combined to process final container batches that represent (b) (4) of starting plasma.

Table 2. Approximate Batch Size of IGSC, 20%

(b) (4)

Information Provided on Drug Product Manufacture: Process Validation

Appropriate in-process controls related to the final manufacturing steps as follows (Table 4, below). The in-process controls include a (b) (4)

Table 3: In Process Controls, Downstream Manufacture IGSC, 20%

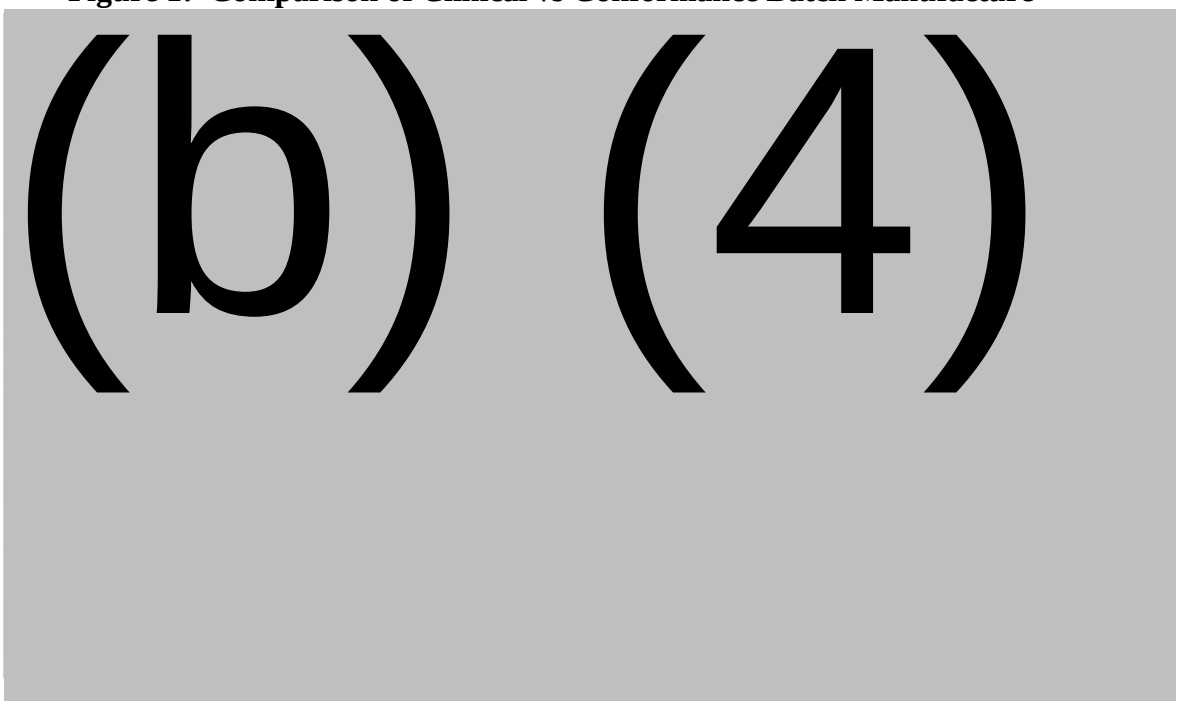
(b) (4)

Conformance Lot Manufacture: The Applicant notes that upstream steps were previously validated in studies submitted and reviewed to support Gammagard Liquid. Therefore the Applicant used (b) (4) See Figure 1 below. The differences between clinical and conformance batch manufacture were discussed with FDA in a type C meeting in November 2014. FDA agreed that these differences would not confound the interpretation of the clinical study. Deviations encountered during preparation of the conformance batches included a lower than target final protein concentration and reduced flow rate during sterile filtration (called "clogging" in the actual study) (b) (4) . Investigations and corrective actions associated with these deviations were reviewed and found acceptable by FDA in November 2014.

Table 4: Information on IGSC, 20% Conformance Study Lots

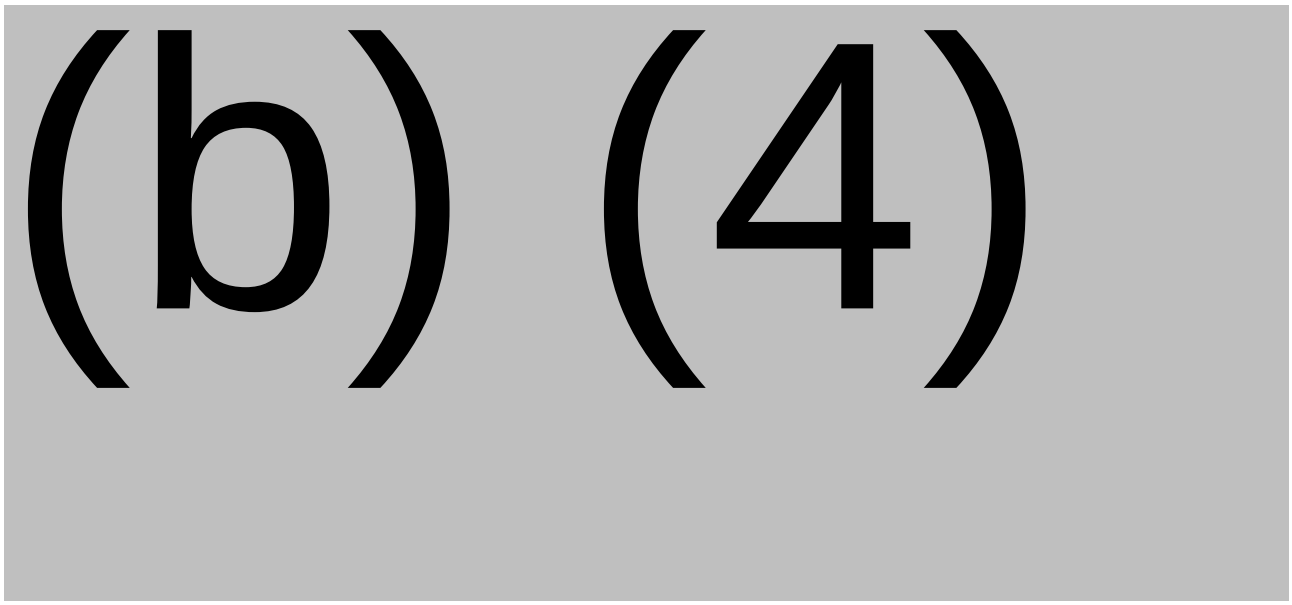
(b) (4)

Figure 1: Comparison of Clinical vs Conformance Batch Manufacture



Study VP-TS-DIV-15-001 (March 6, 2015) details the comparability assessment of IGSC, 20% final container lots. No differences were observed in product characteristics such as (b) (4) , total protein, identity or purity. Contaminants such as residual solvent and detergent were similarly very low in all batches. Titers of specific antibodies were not different across all (b) (4) batches of IGSC, 20% (Figure 2, below).

Figure 2: Comparison of Clinical and Conformance IGSC 20% Lots



1 page has been determined to be not releasable: (b)(4)

(b) (4)

Release Specifications:

Appearance: Product has "light-brown" added as an allowable visual inspection characteristic, based on the Applicant's evaluation of the clinical lots. There is no mention if the conformance lots were "light-brown". This is different from the description of IGI, 10%. Yellow-brown was an approved characteristic for Hizentra (CSLB 20% IGSC).

(b) (4) of Most Other Specifications: Limits both for antibody specificities and for undesirable contaminants (IgA, (b) (4), residual S/D) are (b) (4) the specification for the 10% product. Exceptions are sterility, (b) (4), identity, protein identity, purity, glycine, pH, and bacterial endotoxin ((b) (4)).

Stability Properties: Clinical versus conformance lots, 25°C (b) (4). In each graph, clinical lots are shown in blue and conformance lots are in black. Stability data the Applicant collected at5oC demonstrated no change in stability indicating parameters. Data collected at 25°C (b) (4) are shown. Clinical and conformance lots demonstrated similar stability profiles, with trend toward worse stability at (b) (4) as expected.

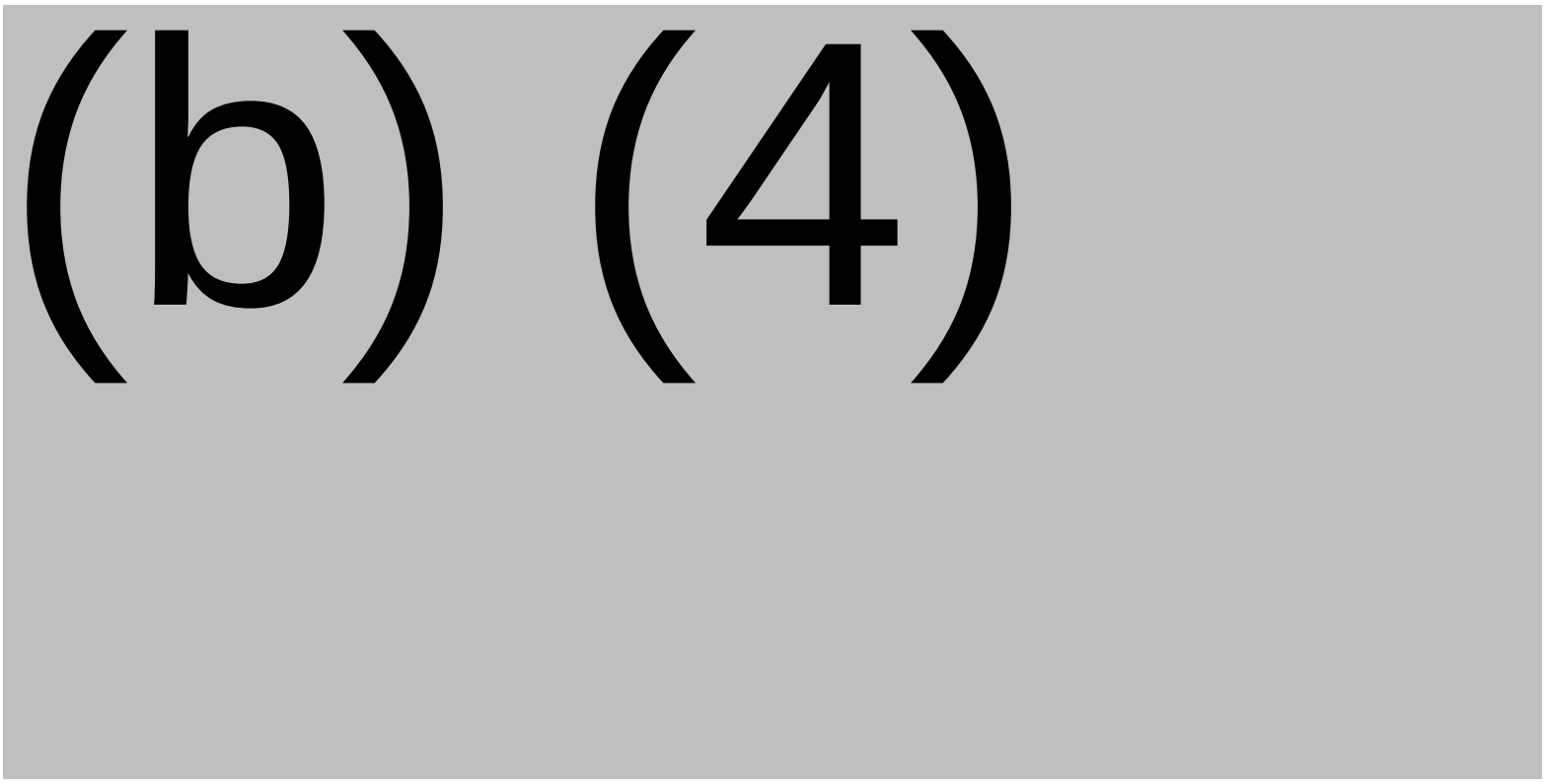
(b) (4)

(b) (4)

Overall the data suggest that the clinical lots and the conformance lots have similar stability properties despite the fact they were manufactured in separate campaigns. Separately, stability data for IGI, 10% and IGSC, 20% data were compared. As expected, the higher concentration product demonstrated worse stability parameters. However the parameters we analyzed at 25oC remained well within specification. Representative data comparing 10% and 20% product are shown at left.

(b) (4)

Potency of IGSC, 20%: Stability Data



Potency measures appeared similar between clinical and conformance IGSC, 20% lots. As expected, (b) (4) over time was faster at (b) (4) than at 25°C.

Stability Conclusions: The increased concentration in the IGSC, 20% product results in a minor change in visual appearance upon reconstitution. An analysis of stability data demonstrated slightly but (b) (4) in the 20% product compared with IGI, 10%. The stability data together adequately support the Applicant's proposed storage:
36 months from the date of manufacture when stored at 5°C.
12 months from the date of manufacture when stored at 25°C/(b) (4).
The Applicant notes its intention to revise the shelf life at 25oC as additional data are collected.

The submission and response from the first IR (125596/0.1 received on 10-14-2015) have been reviewed. A second IR is being prepared for more information and clarification on the sterility and endotoxin test results provided in 125596/0.1.

Currently the (b) (4) validation is incomplete and is directly associated with the quality and control of this drug product. Whether a PMC is necessary will depend on the IR responses.

The lot release protocol template is with the chair for review. A request for samples and reagents to perform (b) (4) testing was sent on 10-Feb-2016; we requested that the reagents and samples

be sent for receipt by 25-Feb-2016. The lot release testing plan draft will be completed and sent for review by 24-Feb-2016.

Pharmacology/Toxicology:
There are no pharmacology/toxicology issues that would prevent this application from being approved.

Clinical Pharmacology:
The pharmacokinetic studies are not yet complete reviewed. Currently there are no clinical pharmacology issues that would prevent this application from being approved.

Clinical:
The primary trial, Study 170904, was a phase 2/3 prospective open-label non-controlled study in the U.S. and Canada to evaluate the safety, efficacy, tolerability and PK of IGSC 20%, Cuvitru. The manufacturing of Cuvitru is based on the currently licensed liquid immunoglobulin Baxalta product Immune Globulin Infusion (IGI, Human), 10% Solution, marketed under the trade name GAMMAGARD LIQUID for IV and SC replacement therapy of PIDD (U.S. and Canada) or Kiovig (European Union).

The primary objective was to evaluate the efficacy of Cuvitru in preventing the development of acute serious bacterial infections in subjects with primary immunodeficiency diseases (PIDDs). Subjects were required to have a documented diagnosis of a form of primary humoral immunodeficiency involving defective antibody formation requiring gammaglobulin replacement.

The study consisted of 4 epochs. In the first epoch, subjects received IGIV, 10%. In Epoch 2, subjects received IGSC, 20% at 145% of the IV dose. The AUC of the dose from Epoch 2 was used to develop an adjusted dose by comparing it to the AUC of Epoch 1. This adjusted dose was then administered in Epoch 3. Individual IgG troughs were then used to determine individually adapted doses which were administered in Epoch 4. Of 86 screened subjects, 74 received IGSC, 20% and 67 subjects completed the trial. The 7 subjects who did not complete the trial primarily withdrew primarily for reasons such as relocating or intolerance of subcutaneous infusions.

The primary endpoint was the rate of acute serious bacterial infections (ASBIs), defined as the mean number of ASBIs per subject per year in the intent-to-treat (ITT) population. There was one ASBI in a 78 year old white male while receiving IGSC, 20%. The point estimate of the annualized rate of ASBIs was 0.01 (upper limit of 99% CI, 0.02) for all study Epochs combined. This rate compares favorably to the FDA recommended threshold of 1.0 ASBI/year. Other adverse events in the study were largely related to infusion site erythema/pain or headache. Secondary endpoints such as the point estimates of annual rate of days missed from school/work or days on antibiotics compared favorably with IGIV, 10% treatment.

The application includes two other studies. Study 170903 was a prospective open label, non-controlled multi-center study in Europe. Of 49 subjects enrolled, 48 of whom were treated with Cuvitru, 45 completed the study. Of the three subjects who did not complete the study, two

withdrew due to intolerance of subcutaneous infusions and the third for logistical issues. The primary endpoint was the same as Study 170903; there were two acute serious bacterial infections of pneumonia in one subject, and no significant safety issues.
The third study included, Study 160601, was a supportive study that did not involve treatment with Cuvitru. The study evaluated the tolerability of IGIV, 10% given subcutaneously to subjects with primary immunodeficiency diseases.

No significant issues were identified in the BLA that would preclude approval.

Epidemiology:
There are no substantive issues that will impact the review timeline or approval action.

Pharmacovigilance Plan (PVP)
Applicant provides an assessment of the important identified risks and potential risks and missing information (Table 1) and proposes routine pharmacovigilance and labeling. Routine pharmacovigilance involves adverse event (AE) reporting in accordance with 21 CFR 600.80. Spontaneous AE reports will be captured in the Baxalta database BASIS (Baxalta Safety Information System). The available data do not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. At this time, routine pharmacovigilance is adequate as per Baxalta's proposed Pharmacovigilance Plan Version 1.0 dated September 1, 2015.

Table 1: Summary of Safety Concerns and Proposed Actions
[Source: BLA submission, module 1.16 PVP, page 46]

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**
Important identified risks	
Interference with serological tests after infusion on immunoglobulin	Routine Pharmacovigilance
Altered immune response to live attenuated vaccines and implications for laboratory testing: Reduced efficacy of live attenuated vaccines such as measles, mumps, rubella, and varicella	Routine Pharmacovigilance
Important potential risks	
Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and EgA antibodies	Routine Pharmacovigilance
Hemolysis/hemolytic anemia	Routine Pharmacovigilance
Thromboembolic events	Routine Pharmacovigilance
Transmission of infectious agents	Routine Pharmacovigilance
Severe renal adverse reactions including renal failure	Routine Pharmacovigilance
Aseptic meningitis syndrome	Routine Pharmacovigilance
Missing information	
Lack of information on safety in pregnant and lactating women	Routine Pharmacovigilance
Limited information on safety in neonates or infants <2 years old	Routine Pharmacovigilance
Limited information in patients with organ impairment (e.g., kidney, liver, or cardiac)	Routine Pharmacovigilance
Limited information on safety in elderly patients 65 and older	Routine Pharmacovigilance

Statistical:
The following areas are not completely reviewed to-date:
5.3.5.3 Integrated summary of safety
5.3.5.3 Integrated summary of efficacy

- Section 3. “Comparison and analyses of efficacy results across studies”
- Section 4. ”Comparison of results in subpopulations” (in studies 170904 and 170903)

There are no major issues at the time of mid-cycle.

The primary efficacy endpoint of pivotal study 170904 was the mean number of validated acute serious bacterial infections (VASBIs) per subject per year in the intent-to-treat (ITT) population with primary immunodeficiency disease (PIDD). The annualized rate of VASBIs (0.012, upper limit of 99% CI: 0.024) during IGSC, 20% treatment (Epoch 2 to Epoch 4) was statistically significantly lower than the historical rate of 1.0 VASBIs/year, ($p<0.0001$). One VASBI of pneumonia was reported during IGSC, 20% treatment in Epoch 4 in a subject who had specific antibody deficiency.

The primary efficacy endpoint of study 170903 was the same as in study 170904. The point estimate of the annualized rate of VASBIs for IGSC, 20% (0.022, upper limit of 99% CI: 0.049) was statistically significantly lower than the historical rate of 1.0 VASBI /year, ($p<0.0001$).

Bioresearch Monitoring:
Bioresearch Monitoring issued two clinical investigator inspection assignments for protocol 170904, clinical study of immune globulin subcutaneous (Human), 20% solution (IGSC, 20%) for the evaluation of efficacy, safety, tolerability and pharmacokinetics in subjects with primary immunodeficiency diseases. The inspections are still pending in the ORA district office.

BIMO will complete the discipline review after the EIR for the inspection have been received.

No BIMO findings or substantive issues to report at this time.

2. Discussion Summary (Other):

- Discipline Review Letters will not be issued.
- The application will not be discussed with the Blood Products Advisory Committee.
- Postmarketing Commitments (PMCs)/Postmarketing Requirements (PMRs) decision will depend on response to outstanding IRs.
- Risk Evaluation Mitigation Strategy (REMS) is not needed.
- National Drug Code (NDC) assignments are still under review.
- Proper naming convention: Immune Globulin Subcutaneous (Human), 20% Solution
- Unique ingredient identifier (UNII) code process has been initiated.
- Pediatric Review Committee (PeRC) meeting has been requested and materials provided.

3. Major target and milestone dates:

Mid-Cycle Communication Telecon: March 4, 2016 (Tentative)
PeRC Meeting: March 9, 2016
Late-Cycle Meeting: May 25, 2016 (Tentative)
Action Due Date: September 13, 2016

4. Mid-cycle Communication Summary:

1. Significant issues/major deficiencies identified by the review committee to date.

- There are no significant / major deficiencies have been identified at this time.

2. Major safety concerns.

- There are no major safety concerns that have been identified at this time.

3. Preliminary review committee thinking regarding risk management.

- Overall the review team considers the product to represent relatively low risk due to 1) the high similarity of the manufacturing process to manufacturing of the licensed IGI, 10%; 2) specific antibodies content, (b) (4) , and impurities are consistent across clinical and conformance lots; 3) acceptable stability profile.
- Most important risk to the product is determined to be variability in (b) (4) characteristics. This critical intermediate is prepared at different facilities, (b) (4) which have demonstrated some variability in the past. Proposed risk management strategies are the same as currently in place for IGI, 10%.
- Please note that (b) (4) and (b) (4) data in this submission are not interpretable as presented.

4. Information requests sent with responses not received

- February 25, 2016 IR requesting SAS program for studies 170903 and 170904 (response due March 3, 2016) – may be received by MC Commination

5. New information requests to be communicated

- Regarding NAPTT and TGT assays: Please report (b) (4) , along with the values for controls and (b) (4) IGIV samples to plasma control. Please provide several dilutions of IGIV ((b) (4)). Please calibrate the (b) (4) assay using the (b) (4) standard and report the lower limit of detection I mIU (b) (4) .

6. **Proposed date(s) for the late-cycle meeting**

    - Presently scheduled for May 19, 2016, 3 pm – 4:30 pm, EST
        - May be rescheduled depending on availability
        - Baxalta may elect to cancel the late-cycle meeting or convert to an alternative format (i.e. teleconference)

7. **Updates regarding plans for the Advisory Committee (AC) meeting**

    - This application will not be referred to the Blood Products Advisory Committee

8. **Other projected milestone dates for the remainder of the review cycle**

    - Labeling negotiation will take place after the late-cycle meeting (May 19, 2016)
    - The action due date is September 13, 2016

END